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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 26-MAR-2009

SUBJECT: **Spirotetramat**. Human-Health Risk Assessment for Proposed Section 18 Emergency Exemption Use on Dry Bulb Onion.

PC Code: 392201
Decision No.: 405486
Petition No.: 09NY02

DP Barcodes: D362206
Registration No.: 264-1050
Regulatory Action: Section 18 Emergency Exemption
Case No.: NA

Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

CAS No.: 382608-10-8
40 CFR: 180.641

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INTRODUCTION

In accordance with 40 §CFR 166.20, the state of New York (NY) proposes a Section 18 Specific Emergency Exemption for the use of spirotetramat (cis-3-(2,5-dimethlyphenyl)-8-methoxy-2-oxo-1-azaspiro [4.5] dec-3-en-4-yl-ethyl carbonate) on dry bulb onions to control onion thrips (*Thrips tabaci*). The proposed program will entail the application of a maximum of 1,016 gallons of Movento™ [EPA Reg. No. 264-1050; a 2 pound (lb) active ingredient (ai)/gallon (gal) suspension-concentrate (SC) formulation] on no more than 13,000 acres of dry bulb onions between June 1, 2009 and September 15, 2009. Two applications per year are allowed under the exemption.

Read RRC 3/27/09

NOTE: HED recently completed a Section 3 risk assessment for the use of spirotetramat on several commodities (Memo, J. Tyler *et al.*, 4/16/08; D333437). This document contains only those aspects of the risk assessment which are affected by the addition of this requested use of spirotetramat on dry bulb onions. The following information from the last risk assessment on spirotetramat can be applied directly to this action (Memo, J. Tyler, *et al.* 4/16/08; D333437):

- Identification of Active Ingredient and Physical and Chemical Properties (Sections 2.2 and 2.3; pp. 13-15);
- Hazard Characterization and Dose-Response Characterization (Section 3.1; pp. 15-17);
- Hazard Identification and Toxicity Endpoint Selection (Section 3.3; pp. 19-22; See Attachment 2 for pertinent toxicology tables);
- Endocrine Disruption (Section 3.4; pp. 22-23);
- Public Health and Pesticide Epidemiology Data (Section 4.0; p.23);
- Pesticide Metabolism and Environmental Degradation (Sections 5.1.1-5.1.9; pp. 23-29);
- Drinking Water Residue Profile (Section 5.1.9; pp. 29-30; summary provided below);
- Dietary Exposure and Risk (Section 5.2; pp. 30-32; summary provided below);
- Aggregate Risk Assessments and Risk Characterization (Section 7.0; p. 33; summary provided below);
- Cumulative Risk Assessment (Section 8.0; p. 34);
- Occupational Exposure Assessment (Section 9.0; pp. 34-37; summary provided below).

SUMMARY

Spirotetramat is a tetramic acid derivative (ketoenole), and is active against sucking insects in vegetables, citrus, pome fruit, stone fruit, grapes, cotton and other plants. It is systemic (xylem and phloem mobile) and can control hidden pests and protect new shoots. Tolerances are currently established under 40 CFR §180.641 for residues of spirotetramat in or on several raw agricultural commodities (RACs), including imported onion, bulb, subgroup 3A-07, and livestock commodities. In addition, there are currently no registered or proposed residential uses for spirotetramat.

The toxicology, chemistry and occupational exposure databases are adequate to support the proposed use of spirotetremat on dry bulb onions. The currently established tolerance of 0.30 ppm for residues of spirotetramat and its metabolites BYI 08330-enol (cis-3-(2,5-dimethylphenyl)-4-hydroxy-8-methoxy-1-azaspiro 4.5 dec-3-en-2-one), BYI 08330-ketohydroxy (cis-3-(2,5-dimethylphenyl)-3-hydroxy-8-methoxy-1-azaspiro 4.5 decane-2,4-dione), BYI08330-enol-Glc (cis-3-(2,5-dimethylphenyl)-8-methoxy-2-oxo-1-azaspiro 4.5 dec-3-en-4-yl beta-D-glucopyranoside), and BYI 08330-mono-hydroxy (cis-3-(2,5-dimethylphenyl)-4-hydroxy-8-methoxy-1-azaspiro 4.5 decan-2-one), calculated as spirotetramat equivalents, in or on onion, bulb, subgroup 3A-07, is adequate to support the Section 18 Emergency Exemption Use.

EXPOSURES AND RISKS

Food Quality Protection Act (FQPA) Considerations: In examining aggregate exposure, the FQPA directs EPA to consider available information concerning exposures from pesticide

residues in food and all other non-dietary, non-occupational exposures (i.e., residential). After review by HED's Hazard Science Policy Council (HASPOC), the spirotetramat risk assessment team recommends that the FQPA safety factor (SF) be reduced to 1X for the following reasons:

- There was no evidence of increased susceptibility of offspring following pre- or post-natal exposure in any study. In the rat developmental toxicity study, toxicity to offspring was observed at the same dose as maternal toxicity, which was also the limit dose. In the developmental toxicity study in the rabbit, only maternal toxicity was observed. In both reproductive toxicity studies, toxicity to offspring (decreased body weight) was observed at the same dose as parental toxicity. Therefore, no evidence of increased susceptibility of offspring was found across four relevant toxicity studies with spirotetramat.
- Spirotetramat does not operate by way of a neurotoxic mechanism of action in target pests.
- Spirotetramat is not considered a neurotoxic chemical in mammals. Clinical signs of toxicity and decreased motor activity were observed in adult rats following a single dose of spirotetramat in the acute neurotoxicity study in the rat; however, these effects only attained statistical significance at high doses and were not observed at the limit dose in the acute oral toxicity study in the rat.
- There is no concern for neurotoxicity with spirotetramat in the developing animal based on the fact that brain dilation in the one-year dog study is most likely a congenital anomaly (see section 3.1.2 of previous risk assessment) that was not observed in any other study in the database, and the fact that the structurally related Bayer compounds spirodiclofen and spiromesifen are not neurotoxic in adults or young.
- There are no residual uncertainties with respect to exposure data. The dietary food exposure assessment utilizes recommended tolerance-level residues and 100% crop treated (CT) information for all proposed commodities. By using this screening-level assessment, the acute and chronic exposures/risks will not be underestimated.
- The dietary drinking water assessment (Tier 1 estimates) utilizes values generated by model and associated modeling parameters which are designed to provide conservative, health-protective, high-end estimates of water concentrations.
- There are no registered or proposed uses of spirotetramat which would result in residential exposure.

EPA began requiring functional immunotoxicity testing of all food and non-food use pesticides on December 26, 2007. Since this requirement went into effect after the tolerance petition was submitted, these studies are not yet available for spirotetramat. In the absence of specific immunotoxicity studies, EPA has evaluated the available spirotetramat toxicity data to determine whether an additional database uncertainty factor is needed to account for potential immunotoxicity. In a 90-day oral toxicity study in dogs, reduced thymus size was observed in females at the highest dose tested, and in a 1-year oral toxicity study in dogs, histopathology of the thymus (thymus involution) was observed with dose-related severity in one male each at the mid and high doses. Because no effects on the thymus were observed in any toxicity study in rodents, EPA does not believe that conducting immunotoxicity testing in rats or mice (the species of choice for immunotoxicity testing) will result in a no-observed adverse-effect level (NOAEL) less than the NOAEL of 5 mg/kg/day already used to calculate the chronic reference dose (cRfD) for spirotetramat, and an additional factor [database uncertainty factor (UF_{DB})] for database uncertainties is not needed to account for potential immunotoxicity.

Subchronic neurotoxicity testing is also required as a result of changes made to the pesticide data requirements in December of 2007. Although a subchronic neurotoxicity study has not yet been submitted, based on data submitted so far, spirotetramat is not considered a neurotoxic chemical. Therefore, EPA has concluded that an additional uncertainty factor is not needed to account for the lack of these data.

Residue Chemistry: The state of NY is requesting application of Movento™ (a 2 lb ai/gal liquid product) intended for foliar applications to dry bulb onions for the control of onion thrips (see Attachment 1). A total of two applications of Movento™ is requested at 0.08 lb ai/A/application for a maximum seasonal application rate of 0.16 lb ai/A. The retreatment interval (RTI) and preharvest interval (PHI) are 7 days. Applications are to be made with air or ground equipment. A rotational crop restriction is included on the label. The application scenario is adequately described.

Nature of the Residue - Plants and Livestock: The nature of the residue in plants, rotational crops, and livestock is adequately understood based on acceptable metabolism studies conducted on apple, lettuce, cotton, potato, rotational crops, lactating goats, and laying hens (Memo, G. Kramer, 4/17/08, D339694). The residues of concern for the tolerance expression and risk assessment for plant commodities are spirotetramat and its metabolites BYI 08330-enol, BYI 08330-ketohydroxy, BYI08330-enol-Glc, and BYI 08330-mono-hydroxy (Memo, J. Tyler *et al.*, 4/16/08; D333437).

Storage Stability: No frozen storage stability data were submitted in support of this Section 18 Emergency Exemption request. Total spirotetramat residues are known to be stable (<30% degradation) in all matrices during freezer storage for up to 718 days. These data support the storage conditions and intervals of samples collected from the bulb vegetable crop field trials as well as the rotational crop studies.

Magnitude of the Residue: No new magnitude of the residue data were submitted in support of this Section 18 request. The results of 8 previously submitted residue trials conducted in Europe were cited in the Section 18 request. These data were submitted and reviewed by HED in conjunction with a request for a tolerance for residues of spirotetramat on onions imported from Europe (Memo, G. Kramer, 4/17/08, D339694). A total of 4 applications were made at a rate of 0.064 lb ai/A, for a total application rate of 0.26 lb ai/A (1.6x the maximum proposed application rate). Samples were collected before the last treatment, 0, 3, 7, 14, and 21 days after the last application. Total spirotetramat residues (spirotetramat and its metabolites BYI 08330-enol, BYI 08330-ketohydroxy, BYI 08330-mono-hydroxy, and BYI 08330-enol-Glc) at a 7-day PHI were <0.054-0.202 ppm (8 field trials in northern Europe) and <0.054-0.172 ppm (8 field trials in southern Europe). As a result, a tolerance of 0.30 ppm for the combined residues of spirotetramat, BYI 08330-enol, BYI 08330-ketohydroxy, BYI 08330-mono-hydroxy, and BYI 08330-enol-Glc, expressed as parent equivalents, in/on onion, bulb, subgroup 3A-07 was established. The previously submitted field trial data are adequate to support the proposed Section 18 use on dry bulb onion, and the current tolerance of 0.30 ppm is adequate.

Magnitude of the Residue - Livestock: As onions are not considered to be ruminant or poultry feed items, a discussion of magnitude of the residue in livestock is not pertinent to this Section 18 request.

Residues in Rotational Crops: The previously submitted field rotational crop data are adequate to support a rotational crop restriction of 30 days for all non-labeled crops.

Analytical Enforcement Method and Multiresidue Method (MRM): Adequate enforcement

methods are available for determination of spirotetramat and metabolites BYI 08330-enol, BYI 08330-ketohydroxy, BYI 08330-mono-hydroxy, and BYI 08330-enol-Glc in plant matrices by high-performance liquid chromatography with positive-ion electrospray tandem mass spectrometry (HPLC-MS/MS) (Method 00857). HED has determined that Method 00857 is a suitable enforcement method for plant and livestock commodities, respectively, since the method passed a successful petition method validation (PMV) by Agency chemists at the Analytical Chemistry Laboratory/Biological and Economics Analysis Division (ACL/BEAD) (E-mail, C. Stafford to D. Vogel; 2/19/08).

Spirotetramat and five metabolites BYI 08330-enol, BYI 08330-ketohydroxy, BYI 08330-mono-hydroxy, BYI 08330-enol-Glc, and BYI 08330-enol-GA have been screened through MRM described in the U.S. Food and Drug Administration (FDA) Pesticide Analytical Manual, Vol. I (PAM I). The MRMs are not suitable for the analysis of spirotetramat or its metabolites. The MRM testing data will be forwarded to FDA for further evaluation and inclusion of results in PAM Vol. I.

Dietary Risks from Food and Drinking Water: The Environmental Fate and Effects Division (EFED) provided Tier 1 ground and surface water estimated drinking water concentration (EDWCs) values for spirotetramat and its major transformation products spirotetramat-enol and spirotetramat-ketohydroxy (Memo, J. Meléndez, 1/22/08, D345275). The ground water EDWCs are based on the use of spirotetramat on pome fruit (0.4 lb ai/A/year); and the surface water EDWCs are based on the use of spirotetramat on Christmas trees (0.32 lb ai/A/year). The total surface water EDWCs (spirotetramat and transformation products of concern) are 0.212 ppb (acute) and 1.37×10^{-3} ppb (chronic). The acute and chronic groundwater EDWC is 3.96×10^{-4} ppb.

As no new tolerances are needed to support the proposed Section 18 use, a new dietary exposure assessment was not conducted. In conjunction with the 4/16/08 risk assessment (Memo, J. Tyler *et al.*, 4/16/08; D333437), acute and chronic dietary exposure analyses were conducted using the Dietary Exposure Evaluation Model-Food Commodity Intake Database (DEEM-FCID™; ver. 2.03) program which incorporates consumption data from the United States Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996/1998. The acute analysis assumed 100% CT and tolerance-level residues for all foods. Empirical and DEEM™ (ver. 7.81) default processing factors were used for processed commodities. A conservative chronic dietary assessment assuming tolerance-level residues, empirical and DEEM™ (ver. 7.81) default processing factors, and 100% CT was also conducted. Drinking water was incorporated directly in the dietary assessment using the acute or chronic concentrations for surface water generated by the FQPA Index Reservoir Screening Tool (FIRST) model. The acute dietary exposure estimates (95^{th} percentile) are not of concern to HED (<100% of the aPAD) for the general U.S. population (4.2% of the aPAD) and all other population subgroups. The most highly exposed population subgroup is children 1-2 years old at 10% of the aPAD. The chronic dietary exposure estimates are not of concern to HED (<100% of the cPAD) for the general U.S. population (28% of the cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-2 years old at 77% of the cPAD.

Aggregate Risks: As no new tolerances are needed to support the proposed Section 18 use, and there is no change to the most recent dietary exposure assessment, a new aggregate risk assessment was not conducted. In conjunction with the most recent human-health risk assessment (Memo, J. Tyler *et al.*, 4/16/08; D333437), human-health aggregate risk assessments have been conducted for the following exposure scenarios: acute aggregate exposure (food + drinking water) and chronic aggregate exposure (food + drinking water). Short- and intermediate-term aggregate risk assessments were not performed because there are no registered or proposed residential uses for spirotetramat. A cancer aggregate risk assessment was not performed because spirotetramat is classified as "Not Likely to be Carcinogenic to Humans." All potential exposure pathways were assessed in the aggregate risk assessment. **All aggregate exposure and risk estimates are not of concern to HED for the scenarios listed above.**

Occupational Exposure and Risk Assessment: An occupational exposure assessment for the use of spirotetramat on citrus, grape and small fruit vine climbing, pome fruit, stone fruit, tree nuts, hops, Christmas trees, cucurbits, fruiting vegetables, leafy vegetables (non-Brassica and Brassica), potato and other tuberous and corm vegetables, and greenhouses/nurseries was provided in a HED memorandum dated 3/13/08 (K. Lowe; DP# 338101). The formulation and application rate assessed for these uses are the same, or higher, as that for the current proposed use. In addition, the equipment used and area treated are expected to be similar. It is believed that the exposure resulting from the current proposed use would not exceed that resulting from the previously assessed use. Therefore, a summary of the previous assessment is presented here.

Occupational Handler Exposure Assessment: In the previous assessment, the following exposure scenarios (pertinent to the current proposed use) were assessed: mixing/loading liquid formulations and applying liquids via ground equipment. None of the handler margins of error (MOEs) calculated were of concern (i.e., all MOEs were greater than the level of concern = 100), provided mixers/loaders wear gloves as required on the product label.

Occupational Post-application Exposure Assessment: In the previous assessment, post-application exposure was assessed for exposure scenarios with higher application rates (0.16 lb ai/A) and transfer coefficients (8000 cm^2/hr), than what would be expected for activities associated with onions (highest transfer coefficient associated with dry onions is 300 cm^2/hr). None of the post-application exposure scenarios resulted in MOEs that were of concern on Day 0 (i.e., all MOEs were greater than the level of concern = 100).

Spirotetramat is classified as Toxicity Category III for acute oral and acute dermal; Toxicity Category II for primary eye irritation; and as Toxicity Category IV for acute inhalation and primary dermal irritation. It is a positive dermal sensitizer. Therefore, while an assessment of systemic toxicity from post-application exposure would indicate acceptable MOEs on the day of treatment, the acute toxicity categories for this chemical require a 24 hour restricted entry interval (REI) for this product under the Worker Protection Standard (WPS). **HED recommends that the REI for all spirotetramat labels have an REI of 24 hours.**

cc (w/ Attachments): J. Tyler, G. Kramer, K. Lowe, R. Mitkus
RDI: RAB1 (3/25/09); G. Kramer (3/25/09); D. Vogel (3/25/09)
J. Tyler: S-10943: Potomac Yard 1 (PY1): (703) 305-5564: 7509P: RAB1

Attachment 1. Summary of Proposed Section 18 Use of Spirotetramat on Dry Bulb Onions.

Crop Site	dry bulb onions in New York
Pest	onion thrips (*Thrips tabaci*)
Formulation	Movento™; EPA Reg. No. 264-1050; 2.0 lb ai/gal liquid
Application Method	foliarly applied, air or ground equipment
Application Rate	0.08 lb ai/A
Application Number	2
Application Maximum	0.16 lb ai/A/yr
RTI	7 days
PHI	7 days
REI	24 hours
Maximum acres treated	13,000 **possible**
Maximum ai used	1,016 gallons active ingredient if all acres are treated at maximum rate
Manufacturer	Bayer

Attachment 2. Toxicology Tables

Acute Toxicity Profile – Spirotetramat Technical				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral (rat)	46904527	LD_{50} >2000 mg/kg (F)	III
870.1200	Acute dermal (rat)	46904529	LD_{50} >2000 mg/kg (M&F)	III
870.1300	Acute inhalation (rat)	46904530	LC_{50} >4.183 mg/L (M&F)	IV
870.2400	Primary eye irritation (rabbit)	46904531	Corneal opacity and iritis (grade 1); cleared by day 8	II
870.2500	Primary dermal irritation (rabbit)	46904532	Negative	IV
870.2600	Dermal sensitization (mouse)	46904565	Positive (LLNA)	N/A

Subchronic and Chronic Toxicity and Genotoxicity Profile – Spirotetramat Technical.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	28-Day oral toxicity (mouse)	46904536 (2001) Acceptable/non-guideline 0, 500 or 5000 ppm (equivalent to 0, 136.5 or 1415 mg/kg bw/day [M])	NOAEL = 5000 ppm (1415 mg/kg/day [M]). LOAEL not observed.
870.3100	90-Day oral toxicity (mouse)	46904539 (2005) Acceptable/guideline 0, 70, 350, 1700, or 7000 ppm (equivalent to 0/0, 12.8/16, 59.6/72.4, 300/389 or 1305/1515 mg/kg bw/day [M/F])	NOAEL = 7000 ppm (1305/1515 mg/kg/day [M/F]). LOAEL not observed.
870.3100	28-Day oral toxicity (rat)	46904537 (1998) Acceptable/non-guideline 0, 500 or 5000 ppm (equivalent to 0, 47.3 or 501.8 mg/kg bw/day [F])	NOAEL = 5000 ppm (501.8 mg/kg/day [F]). LOAEL not observed.
870.3100	90-Day oral toxicity (rat)	46904538 (2005) Acceptable/guideline 0, 150, 600, 2500, or 10000 ppm (equivalent to 0/0, 9/11, 26/46, 148/188 or 616/752 mg/kg bw/day [M/F])	NOAEL = 2500 ppm (148/188 mg/kg/day [M/F]). LOAEL = 10000 ppm (616/752 mg/kg/day [M/F]), based on decreased body weight, abnormal spermatozoa and hypospermia in the epididymis, decreased testicular weight, and testicular degeneration and vacuolation in males; and alveolar macrophages in both sexes.
870.3150	28-Day oral toxicity (dog)	46904572 (2004) Acceptable/non-guideline 0, 100, 400, 1600, or 6400 ppm (equivalent to 0/0, 3/3, 13/12, 42/70, or 104/127 mg/kg/day [M/F])	NOAEL = 1600 ppm (42/70 mg/kg/day [M/F]). LOAEL = 6400 ppm (104/127 mg/kg/day [M/F]) based on decreased thymus size and weight as well as decreased body weight and food consumption, which resulted in emaciation.
870.3150	90-Day oral toxicity (dog)	46904541 (2005) Acceptable/guideline 0, 150, 300, 1200, or 4000/2500 ppm (equivalent to 0/0, 5/6, 9/10, 33/32, or 81/72 mg/kg bw/day)	NOAEL = 1200 (32 mg/kg/day)[F] & 2500 ppm (81 mg/kg/day)[M]. LOAEL = 2500 ppm (72 mg/kg/day)[F] based on decreased body-weight gain and food consumption, depressed RBC parameters (red blood cell count, hemoglobin level and hematocrit), and thymus atrophy.

870.3200	28-Day dermal toxicity (rat)	46904542 (2006) Acceptable/guideline 0, 100, 300, or 1000 mg/kg bw/day (limit dose)	NOAEL = 1000 mg/kg/day. LOAEL not established.
870.3700a	Prenatal developmental (rat)	46904543 (2004) Acceptable/guideline 0, 20, 140, or 1000 mg/kg bw/day	**Maternal** NOAEL = 140 mg/kg/day. LOAEL = 1000 mg/kg/day based on impaired food consumption, transient body weight loss, impaired body-weight gain, and reduced final body weight. **Developmental** NOAEL = 140 mg/kg/day. LOAEL = 1000 mg/kg/day based on reduced fetal weight and increased incidences of malformations and skeletal variations.
870.3700b	Prenatal developmental (rabbit)	46904544 (2004) Acceptable/guideline 0, 10, 40 or 160 mg/kg bw/day	**Maternal** NOAEL = 10 mg/kg/day. LOAEL = 40 mg/kg/day based on late abortion (≥GD 22), clinical signs, impaired food and water consumption and body weight loss. **Developmental** NOAEL = 160 mg/kg/day. LOAEL not observed.
870.3800	1-gen. reproduction and fertility effects (rat) – range finding	46904571 (2006) Acceptable/non-guideline 0, 200, 500, 6000 or 10000 ppm (equivalent to 0/0, 10.5/12.8, 27.8/31.4, 320.1/384.1, or 537.9/645.7 mg/kg bw/day [M/F])	**Parental/Systemic** NOAEL = 500 ppm (27.8 and 31.4 mg/kg bw/day [M/F]). LOAEL = 6,000 ppm (320.1 and 384.1 mg/kg bw/day [M/F]) based on decreased body-weight gain (P females) and terminal body weight (F_1 males). **Reproductive** NOAEL = 500 ppm (27.8 mg/kg bw/day [M]) and 10,000 ppm (645.7 mg/kg/day) [F]. LOAEL = 6,000 ppm (320.1 mg/kg bw/day [M]) based on decreased sperm motility and progression and increased abnormal sperm cells in the F_1 males. **Offspring** NOAEL = 500 ppm (27.8 and 31.4 mg/kg bw/day [M/F]). LOAEL = 6,000 ppm (320.1 and 384.1 mg/kg bw/day [M/F]) based on decreased body weight and body-weight gain during lactation in F_1 pups.
870.3800	2-gen. reproduction and fertility effects (rat)	46904546 (2006) Acceptable/guideline 0, 250, 1,000 or 6,000 ppm (equivalent to 0/0, 17.2/20, 70.7/82.5 or 419.3/484.7 mg/kg bw/day [M/F])	**Parental/Systemic** NOAEL = 1000 ppm (70.7/82.5 mg/kg/day [M/F]). LOAEL = 6000 ppm (419.3/484.7 mg/kg/day [M/F]) based on decreases in body weight (F_1 males and females), weight gain (P males, F_1 males and females), and food consumption during lactation (P- and F_1-generation females); and kidney histopathology and decreased kidney weights (F_1 males and females). **Reproductive** NOAEL = 1000 ppm (70.7 mg/kg/day)[M] & 6000 ppm (484.7 mg/kg/day)[F]. LOAEL = 6000 ppm (419.3 mg/kg/day)[M] based on abnormal sperm cells and decreased reproductive performance in the F_1 males. **Offspring** NOAEL = 1000 ppm (70.7/82.5 mg/kg/day [M/F]). LOAEL = 6000 ppm (419.3/484.7 mg/kg/day [M/F]) based on decreased body weight and body-weight gain during lactation in both F_1 and F_2 generations.
870.4100	Chronic toxicity (1 year; dog)	46904548 (2006) Acceptable/guideline 0, 200, 600 or 1800 ppm (equivalent to 0/0, 6/5, 20/19, or 55/48 mg/kg/day [M/F])	NOAEL = 200 ppm (6 mg/kg/day)[M] & 1800 ppm (48 mg/kg/day)[F]. LOAEL = 600 ppm (20 mg/kg/day)[M] based on thymus involution [M] and not observed [F]..

870.4100	Chronic toxicity (1 year; rat)	46904547 (2005) Acceptable/guideline 0, 250, 3500, or 7500/12000 ppm (M/F) (equivalent to 0/0, 13.2/18, 189/255, or 414/890 mg/kg bw/day [M/F])	NOAEL = 250 ppm (13.2 mg/kg/day)[M] & 3500 ppm (255 mg/kg/day)[F]. LOAEL = 3500 ppm (189 mg/kg/day)[M] based on dose-dependent increase in alveolar macrophages; & 12000 ppm (890 mg/kg/day)[F] based on decreased body weight and body-weight gain, alveolar macrophages, discoloration of the lung, and yellow/brown staining of the perigenital area and tail.
870.4200	Carcinogenicity (rat)	46904549 (2006) Acceptable/guideline 0, 250, 3500, or 7500/12000 ppm (M/F) (equivalent to 0/0, 12.5/16.8, 169/229, or 373/823 mg/kg bw/day [M/F])	NOAEL = 250 ppm (12.5/16.8 mg/kg/day [M/F]). LOAEL = 3500 ppm (169/229 mg/kg/day [M/F]) based on decreased kidney weight and renal tubular dilation. No evidence of carcinogenicity.
870.4200	Carcinogenicity (mouse)	46904550 (2006) Acceptable/guideline 0, 70, 1700 or 7000/6000 ppm (M/F) (equivalent to 0/0, 10.9/13.7, 263/331, or 1022/1319 mg/kg/day [M/F])	NOAEL = 7000/6000 ppm (1022/1319 mg/kg/day [M/F]). LOAEL not observed. No evidence of carcinogenicity.
870.5100	Bacterial Gene Mutation	46904551 (2006) Acceptable/guideline 0, 16, 50, 158, 500, 1581 or 5000 µg/plate +/- S9 activation	Negative.
870.5100	Bacterial Gene Mutation	46904552 (2002) Acceptable/guideline 0, 16, 50, 158, 500, 1581 or 5000 µg/plate +/- S9 activation	Negative.
870.5300	Mammalian Gene Mutation	46904553 (2002) Acceptable/guideline 0, 2.5, 5, 10, 20, 30, 40, 50, 60, 70, or 80 µg/mL (-S9) 0, 20, 40, 60, 80, 92, 100, 108, 116, 120, 124, 132, or 140 µg/mL (+S9)	Negative.
870.5375	In vitro mammalian chromosome aberration	46904554 (2002) Acceptable/guideline 0, 10, 12, 24, 30, 48, or 50 µg/mL (-S9) 0, 20, 40 or 80 µg/mL (+S9)	Weakly clastogenic at cytotoxic concentrations only.
870.5375	In vitro mammalian chromosome aberration	46904555 (2003) Unacceptable/guideline 0, 30, 50, 70, 90 or 110 µg/mL (-S9) 0, 40, 60, 80, 100 or 120 µg/mL (+S9)	N/A
870.5395	*In vivo* erythrocyte micronucleus assay (mouse)	46904556 (2002) Acceptable/guideline 0, 125, 250, or 500 mg/kg bw	Negative.

870.5385	*In vivo* bone marrow chromosomal aberration assay (mouse)	46904558 (2003) Acceptable/guideline 0, 125, 250 or 500 mg/kg bw	Negative.
870.5550	*In vivo/in vitro* UDS assay (rat hepatocytes)	46904557 (2003) Acceptable/guideline 0, 1000, or 2000 mg/kg bw	Negative.
870.6200a	Acute neurotoxicity screening battery	46904560 (2005) Acceptable/guideline 0, 50, 100, 200, 500 or 2000 mg/kg bw	NOAEL = 100 mg/kg/day. LOAEL = 200 mg/kg/day based on clinical signs (males and females) and decreased motor activity (males).
870.7485	Metabolism and pharmacokinetics (rat)	46904504 (2006) Acceptable/guideline 2 or 100 mg/kg bw (single) 2 mg/kg bw (repeat)	Absorption: 89-98% after 48 hrs (no significant differences among low-dose, high-dose, and repeated-dose tests). Distribution: $AUC_{0-\infty}$ (measure of systemic exposure) slightly higher for males than females; <0.2% of administered dose detected in body 48 hrs after sacrifice; highest equivalent concentrations detected in liver and kidney. Metabolism: parent compound undetected in urine and faeces of all tests; main metabolic reaction was cleavage of the ester group which resulted in formation of the primary metabolite BYI 08330-enol (53-87% of administered dose); all other identified metabolites could be derived from enol; male rats exhibited much higher rates of demethylation of BYI 08330-enol to BYI 08330-desmethyl-enol (25-37%) vs. females rats (5-10 %). Excretion: 88-95% of administered dose eliminated via urine and 2-11% via faeces within 48 hrs.
870.7485	Metabolism and pharmacokinetics (rat)	46904561 (2006) Acceptable/guideline 2 or 1000 mg/kg bw (single)	At 1000 mg/kg bw: Absorption and excretion less than low dose, with 27% of dose excreted in urine after 24 hours (18% in feces); plasma radioactivity slightly higher than in liver and kidney; these results are consistent with saturation of cellular transport mechanisms. Tissue radioactivity decreased from 1 h to 24 h post dose. Metabolism profile qualitatively similar to that of the low dose; BYI 08330-enol was most prominent metabolite; similar to low dose group, BYI 08330-desmethyl-enol levels greater in urine than in plasma and organs.
870.7600	*In vivo* dermal penetration (rat)	46904563 (2006) Acceptable/guideline 100, 15, or 5 µg ai/cm^2 (OD150 formulation)	Dermal absorption = 10%.
Special study	Male reproductive toxicity	46904569 (2005) Acceptable/non-guideline 1000 mg/kg bw/day (3, 10, 21 or 41 days)	Primary testicular effects on or after day 10 were degeneration of round and elongating spermatids (stage 7-8 and 9-14, respectively), decreased sperm count, and increased numbers of aberrant/abnormal spermatozoa in the epididymis.

USEPA Toxicity Profile – Enol Metabolite.

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
Exploratory study	10-day gavage (enol metabolite)	46904601 (2006) Acceptable/non-guideline 800 mg/kg bw/day	Decreased BWG; histopathology not evaluated.

USEPA Toxicity Profile – Enol Metabolite.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Special study	21-day gavage (enol metabolite)	47070901 (2006) Acceptable/non-guideline 800 mg/kg bw/day	Clinical signs of toxicity, decreased BWG, testicular/spermatotoxicity.
870.5100	Bacterial Gene Mutation (ketohydroxy metabolite)	46904594 (2005) Acceptable/guideline 0, 16, 50, 158, 500, 1581 or 5000 µg/plate +/- S9 activation	Negative.
870.7485	Metabolism and Pharmacokinetics (rat) (ketohydroxy metabolite)	46904595 (2006) Acceptable/guideline 2 mg/kg bw (single)	Absorption: ≥55% after 48 hrs. Distribution: highest concentrations detected in GI, liver, and kidney; <0.2% of administered dose detected in body 48 hrs post dose. Metabolism: parent compound undetected in urine and trace amounts in faeces; main metabolic reaction was oxidative demethylation of cyclohexyl-O-methyl group to form desmethyl-ketohydroxy metabolite (15% of administered dose); all other identified metabolites could be derived from desmethyl-ketohydroxy metabolite. Excretion: 54% of administered dose eliminated via urine and 44% via faeces within 48 hrs.
870.5100	Bacterial Gene Mutation (desmethyl-ketohydroxy metabolite)	46904597 (2006) Acceptable/guideline 0, 16, 50, 158, 500, 1581 or 5000 µg/plate +/- S9 activation	Negative.
870.5100	Bacterial Gene Mutation (dihydroxy metabolite)	46904599 (2005) Acceptable/guideline 0, 16, 50, 158, 500, 1581 or 5000 µg/plate +/- S9 activation	Negative.
870.7485	Metabolism and Pharmacokinetics (rat) (enol glucoside metabolite)	46904602 (2006) Acceptable/non-guideline 0.1 mg/kg bw (single; 1 rat)	Absorption: 54% after 48 hrs. Distribution: plasma concentrations peaked 4 hrs post dose; 1% of administered dose detected in body 48 hrs post dose. Metabolism: parent compound detected in faeces (21%); main metabolite was enol (64% of administered dose). Excretion: 53% of administered dose eliminated via urine and 44% via faeces within 48 hrs.
870.5100	Bacterial Gene Mutation (monohydroxy metabolite)	46904604 (2005) Acceptable/guideline 0, 16, 50, 158, 500, 1581 or 5000 µg/plate +/- S9 activation	Negative.

Summary of Toxicological Doses and Endpoints for Spirotetramat for Use in Dietary Human-Health Risk Assessments.

Exposure Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Relevant Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	NOAEL = 100 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	aRfD = aPAD = 1.0 mg/kg/day	**Acute neurotoxicity (rat; gavage)** LOAEL = 200 mg/kg based on clinical signs (M&F) and decreased motor activity (M).
Chronic Dietary (All populations)	NOAEL = 5 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	cRfD = cPAD = 0.05 mg/kg/day[1]	**Chronic toxicity (dog; dietary)** LOAEL = 20 mg/kg/day (M) based on thymus involution.
Cancer (oral, dermal, inhalation)	Classification: "Not Likely to be Carcinogenic to Humans" based on lack of evidence of carcinogenicity in two oral rodent carcinogenicity studies.			

Abbreviations: UF = uncertainty factor, UF_A = extrapolation from animal to human (interspecies), UF_H = potential variation in sensitivity among members of the human population (intraspecies), UF_{FQPA} = FQPA Safety Factor, NOAEL = no-observed adverse-effect level, LOAEL = lowest-observed adverse-effect level, RfD = reference dose (a = acute, c = chronic), PAD = population-adjusted dose, MOE = margin of exposure, LOC = level of concern.

[1] The cRfD has been harmonized across American (USEPA), Canadian (PMRA), and Austrian (AGES) regulatory agencies. However, it is noted that USEPA considered a NOAEL=6 mg/kg/day in males and a NOAEL=19 mg/kg/day in females to more accurately reflect the toxicological data. The difference between 5 mg/kg/day (NOAEL in females for PMRA and AGES) and 6 mg/kg/day was considered negligible for risk assessment.

Summary of Toxicological Doses and Endpoints for Spirotetramat for Use in Occupational Human Health Risk Assessments.

Exposure Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short- and Intermediate- Term (1-30 days and 1-6 months)	NOAEL = 10 mg/kg/day Dermal absorption factor = 10%	UF_A = 10X UF_H = 10X	Occupational LOC for MOE <100	**Prenatal developmental toxicity (rabbit)** Maternal LOAEL = 40 mg/kg/day based on late abortion (≥GD 22), clinical signs, impaired food and water consumption and body-weight loss.
Dermal Long-Term (>6 months)	NOAEL = 5 mg/kg/day Dermal absorption factor = 10%	UF_A = 10X UF_H = 10X	Occupational LOC for MOE <100	**Chronic toxicity (dog; dietary)** LOAEL = 20 mg/kg/day (M) based on thymus involution.
Inhalation Short- and Intermediate- Term (1-30 days and 1-6 months)	NOAEL = 10 mg/kg/day 100% inhalation assumed	UF_A = 10X UF_H = 10X	Occupational LOC for MOE <100	**Prenatal developmental toxicity (rabbit)** Maternal LOAEL = 40 mg/kg/day based on late abortion (≥GD 22), clinical signs, impaired food and water consumption and body-weight loss.
Inhalation Long-Term (>6 months)	NOAEL = 5 mg/kg/day 100% inhalation assumed	UF_A = 10X UF_H = 10X	Occupational LOC for MOE <100	**Chronic toxicity (dog; dietary)** LOAEL = 20 mg/kg/day (M) based on thymus involution.
Cancer (oral, dermal, inhalation)	Classification: Not likely to be carcinogenic to humans based on lack of evidence of carcinogenicity in two oral rodent carcinogenicity studies.			

Abbreviations: UF = uncertainty factor, UF_A = extrapolation from animal to human (interspecies), UF_H = potential variation in sensitivity among members of the human population (intraspecies), UF_{FQPA} = FQPA Safety Factor, NOAEL = no-observed adverse-effect level, LOAEL = lowest-observed adverse-effect level, RfD = reference dose (a = acute, c = chronic), LOC = level of concern.

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R168510

Chemical Name: Spirotetramat

PC Code: 392201
HED File Code: 14000 Risk Reviews
Memo Date: 3/26/2009
File ID: 00000000
Accession #: 000-00-0130

HED Records Reference Center
3/30/2009